Claims

What is claimed:

1. A method of preventing bone loss comprising administering to a subject afflicted with a disease that causes or contributes to osteolysis a therapeutically effective amount of M-CSF-specific antibody RX1 set out in Figure 4, or an antibody of any one of claims 10 through 24, thereby preventing bone loss associated with the disease.

2. A method of treating a subject afflicted with a disease that causes or contributes to osteolysis comprising administering to said subject a therapeutically effective amount of M-CSF-specific antibody RX1 set out in Figure 4, or an antibody of any one of claims 10 through 24, thereby reducing the severity of bone loss associated with the disease.

3. The method according to claims 1 or 2 wherein said subject is a mammal.

4. The method according to claim 3 wherein said mammal is human.

5. The method according to claim 4 wherein said antibody inhibits the interaction between M-CSF and its receptor (M-CSFR).

6. The method according to claim 5 wherein said antibody inhibits osteoclast proliferation and/or differentiation induced by tumor cells.

7. The method according claim 6 wherein said disease is selected from the group consisting of Metabolic bone diseases associated with relatively increased osteoclast activity, including endocrinopathies (hypercortisolism, hypogonadism, primary or secondary hyperparathyroidism, hyperthyroidism), hypercalcemia, deficiency states (rickets/osteomalacia, scurvy, malnutrition), chronic diseases (malabsorption syndromes, chronic renal failure (renal osteodystrophy), chronic liver disease (hepatic osteodystrophy)), drugs (glucocorticoids (glucocorticoid-induced osteoporosis), heparin, alcohol), and hereditary diseases (osteogenesis imperfecta, homocystinuria), cancer, osteoporosis, osteopetrosis, inflammation of bone associated with arthritis and rheumatoid arthritis, periodontal disease, fibrous dysplasia, and/or Paget's disease.

8. The method according to claim 7 wherein the metastatic cancer is breast, lung, renal, multiple myeloma, thyroid, prostate, adenocarcinoma, blood cell malignancies, including leukemia and lymphoma; head and neck cancers; gastrointestinal cancers, including stomach cancer, colon cancer, colorectal cancer, pancreatic cancer, liver

cancer; malignancies of the female genital tract, including ovarian carcinoma, uterine endometrial cancers and cervical cancer; bladder cancer; brain cancer, including neuroblastoma; sarcoma, osteosarcoma; and skin cancer, including malignant melanoma or squamous cell cancer.

9. The method according to claim 8 wherein the M-CSF antibody is an antibody administered at a dose between about 2 μg/kg to 10 mg/kg.

10. A non-murine monoclonal antibody or functional fragment thereof, comprising one or more complementary determining regions (CDRs) selected from the group consisting of CDRs 1, 2, 3, 4, 5, and 6 of Figure 4, wherein said non-murine monoclonal antibody or functional fragment thereof specifically binds M-CSF.

11. The antibody according to claim 10 wherein said antibody or functional fragment thereof specifically binds to the extracellular domain of M-CSFα as set in Figure 10.

12. The antibody according to claim 10 wherein said antibody or functional fragment thereof specifically binds M-CSFβ as set in Figure 11.

13. The antibody according to claim 10 wherein said antibody or functional fragment thereof specifically binds M-CSFγ as set in Figure 12.

14. The antibody of claim 10, comprising a variable heavy chain amino acid sequence as set forth in Figure 4.

15. The antibody of claim 10, comprising a variable light chain amino acid sequence as set forth in Figure 4.

16. The antibody of claim 10, comprising a variable heavy chain amino acid sequence which is at least 65, 70, 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% homologous to the amino acid sequence as set forth in Figure 4.

17. The antibody of claim 10, comprising a variable light chain amino acid sequence which is at least 65, 70, 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% homologous to the amino acid sequence as set forth in Figure 4.

18. The antibody of claim 10, comprising at least 2, 3 , 4, 5, or 6 CDRs selected from the group consisting of CDRs 1, 2, 3, 4, 5, and 6 o Figure 4.

19. The antibody of claim 10, comprising a constant region and one or

more heavy and light chain variable framework regions of a human antibody.

20. Antibody RX1 that binds to M-CSF for preventing a subject afflicted with a disease that causes or contributes to osteolysis, wherein said antibody effectively reduces the severity of bone loss associated with the disease.

21. Antibody RX1 that binds to M-CSF for treating a subject afflicted with a disease that causes or contributes to osteolysis, wherein said antibody effectively reduces the severity of bone loss associated with the disease.

22. A non-murine monoclonal antibody that specifically binds to the same epitope of M-CSF as monoclonal antibody RX1.

23. A non-murine monoclonal antibody that competes with monoclonal antibody RX1 for binding to M-CSF more than 75%.

24. The antibody according to claim 22 or 23 wherein the antibody is selected from the group consisting of a polyclonal antibody; a monoclonal antibody; a humanized antibody; a human antibody; a chimeric antibody; Fab, F(ab')2 or Fv antibody fragment; a diabody; or a mutein of any one of these antibodies.

25. The antibody according to claims 20 or 21 wherein said disease is selected from the group consisting of Metabolic bone diseases associated with relatively increased osteoclast activity, including endocrinopathies (hypercortisolism, hypogonadism, primary or secondary hyperparathyroidism, hyperthyroidism), hypercalcemia, deficiency states (rickets/osteomalacia, scurvy, malnutrition), chronic diseases (malabsorption syndromes, chronic renal failure (renal osteodystrophy), chronic liver disease (hepatic osteodystrophy)), drugs (glucocorticoids (glucocorticoid-induced osteoporosis), heparin, alcohol), and hereditary diseases (osteogenesis imperfecta, homocystinuria), cancer, osteoporosis, osteopetrosis, inflammation of bone associated with arthritis and rheumatoid arthritis, periodontal disease, fibrous dysplasia, and/or Paget's disease.

26. The antibody according to claim 25 wherein the metastatic cancer is breast, lung, renal, multiple myeloma, thyroid, prostate, adenocarcinoma, blood cell malignancies, including leukemia and lymphoma; head and neck cancers; gastrointestinal cancers, including stomach cancer, colon cancer, colorectal cancer, pancreatic cancer, liver cancer; malignancies of the female genital tract, including ovarian carcinoma, uterine endometrial cancers and cervical cancer; bladder cancer; brain cancer, including neuroblastoma; sarcoma, osteosarcoma; and skin cancer, including malignant melanoma or

squamous cell cancer.

27. A hybridoma that secretes an antibody according to claim 25.

28. A pharmaceutical composition comprising any one of the antibodies of claims 20 to 27, and a pharmaceutically suitable carrier, excipient or diluent.

29. A method of screening for an M-CSF-specific antibody comprising the steps of:

a) contacting metastatic tumor cell medium, osteoclasts and a candidate antibody;

b) detecting osteoclast formation, proliferation and/or differentiation; and

c) identifying said candidate antibody as an M-CSF-specific antibody if a decrease in osteoclast formation, proliferation and/or differentiation is detected.

30. The method of claim 29 wherein said metastatic tumor cell medium includes tumor cells.

31. The method of claim 29 wherein said contacting step (a) occurs *in vivo*, said detecting step (b) comprises detecting size and/or number of bone metastases, and said candidate antibody is identified as an M-CSF-specific antibody if a decrease in size and/or number of bone metastases is detected.

32. The method of claim 29 further comprising the step of determining if said candidate antibody binds to M-CSF.

33. The method of claim 29 further comprising the step of determining if said candidate antibody inhibits interaction between M-CSF and its receptor M-CSFR.

34. A method of identifying an M-CSF-specific antibody that can prevent or treat metastatic cancer to bone, comprising the steps of:

(a) detecting binding of a candidate antibody to M-CSF; and

(b) assaying the ability of said candidate antibody to prevent or treat metastatic cancer to bone *in vitro* or *in vivo*.

35. A method of identifying an M-CSF-specific antibody that can prevent or treat metastatic cancer to bone, comprising the steps of:

(a) detecting binding of a candidate antibody to M-CSFR; and

(b) assaying the ability of said candidate antibody to prevent or treat metastatic cancer to bone *in vitro* or *in vivo*.

36. A method of identifying an M-CSF-specific antibody that can prevent or treat metastatic cancer to bone, comprising the steps of:

(a) identifying a candidate antibody that inhibits the interaction between M-CSF and M-CSFR; and

(b) assaying the ability of said candidate antibody to prevent or treat metastatic cancer to bone *in vitro* or *in vivo*.

37. A method of preventing bone loss and tumor growth comprising administering to a subject afflicted with metastatic cancer therapeutically effective amounts of antibody RX1 and a therapeutic agent, thereby preventing bone loss associated with the metastatic cancer and preventing tumor growth.

38. A method of treating a subject afflicted with a metastatic cancer comprising administering to said subject therapeutically effective amounts of antibody RX1 and a therapeutic agent, thereby reducing the severity of bone loss associated with the metastatic cancer and inhibiting tumor growth.

39. The method according to claims 37 or 38 wherein said subject is a mammal.

40. The method according to claim 39 wherein said mammal is human.

41. The method according to claim 40 wherein said antibody inhibits the interaction between M-CSF and its receptor M-CSFR.

42. The method according to claim 41 wherein said antibody inhibits osteoclast proliferation and/or differentiation induced by tumor cells.

43. The methods according to claims 37 or 38 wherein the therapeutic agent is a bisphosphonates.

44. The method according to claim 43 wherein the bisphonate is zeledronate, pamidronate, clodronate, etidronate, tilundronate, alendronate, or ibandronate.

45. The methods according to claims 37 or 38 wherein the therapeutic agent is a chemotherapeutic agent.

46. The method according to claim 45 wherein the subject is precluded from receiving bisphophonate treatment.

47. The methods according to claims 37 or 38 wherein the antibody RX1 is effective to reduce the dosage of therapeutic agent required to achieve a therapeutic effect.

48. The methods according to claims 37 or 38 further comprising the step of administering a non-M-CSF colony stimulating factor, for example G-CSF.

49. A pharmaceutical composition comprising antibody RX1 and a cancer therapeutic agent.

50. A package, vial or container comprising a medicament comprising antibody RX1 and instructions that the medicament should be used in combination with surgery or radiation therapy.

51. A method of preventing or treating metastatic cancer to bone comprising the steps of administering antibody RX1 to a subject and treating said subject with surgery or radiation therapy.

52. A method of targeting a tumor cell expressing membrane-bound M-CSF on its surface comprising the step of administering antibody RX1, wherein said antibody is conjugated to a radionuclide or other toxin.

53. A method of treating a subject suffering from a cancer, wherein the cells comprising said cancer do not secrete M-CSF, comprising the step of administering antibody RX1.

54. A method of preventing bone loss comprising administering to a subject afflicted with a disease that causes or contributes to osteolysis an amount of antibody RX1 effective to neutralize M-CSF produced by the subject's cells, said amount being larger than the amount effective to neutralize M-CSF produced by the cancer cells.

55. A method of treating a subject afflicted with a disease that causes or contributes to osteolysis comprising administering to said subject an amount of antibody RX1 effective to neutralize M-CSF produced by the subject's cells, said amount being larger than the amount effective to neutralize M-CSF produced by the cancer cells.